Lentivirus Mediated Correction of Artemis-Deficient Severe Combined Immunodeficiency.

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Public Summary:
During B and T lymphocyte maturation, V(D)J recombination is initiated by creation of DNA double-strand breaks. Artemis is an exonuclease essential for their subsequent repair by nonhomologous end-joining. Mutations in DCLRE1C, the gene encoding Artemis, cause T-B-NK+ severe combined immunodeficiency (ART-SCID) and also confer heightened sensitivity to ionizing radiation and alkylating chemotherapy. Although allogeneic hematopoietic cell transplantation can treat ART-SCID, conditioning regimens are poorly tolerated, leading to early mortality and/or late complications, including short stature, endocrinopathies, and dental aplasia. However, without alkylating chemotherapy as preconditioning, patients usually have graft rejection or limited T cell and no B cell recovery. Thus, addition of normal DCLRE1C cDNA to autologous hematopoietic stem cells is an attractive strategy to treat ART-SCID. We designed a self-inactivating lentivirus vector containing human Artemis cDNA under transcriptional regulation of the human endogenous Artemis promoter (AProArt). Fibroblasts from ART-SCID patients transduced with AProArt lentivirus showed correction of radiosensitivity. Mobilized peripheral blood CD34+ cells from an ART-SCID patient as well as hematopoietic stem cells from Artemis-deficient mice demonstrated restored T and B cell development following AProArt transduction. Murine hematopoietic cells transduced with AProArt exhibited no increase in replating potential in an in vitro immortalization assay, and analysis of AProArt lentivirus insertions showed no predilection for sites that could activate oncogenes. These efficacy and safety findings support institution of a clinical trial of gene addition therapy for ART-SCID.

Scientific Abstract:
During B and T lymphocyte maturation, V(D)J recombination is initiated by creation of DNA double-strand breaks. Artemis is an exonuclease essential for their subsequent repair by nonhomologous end-joining. Mutations in DCLRE1C, the gene encoding Artemis, cause T-B-NK+ severe combined immunodeficiency (ART-SCID) and also confer heightened sensitivity to ionizing radiation and alkylating chemotherapy. Although allogeneic hematopoietic cell transplantation can treat ART-SCID, conditioning regimens are poorly tolerated, leading to early mortality and/or late complications, including short stature, endocrinopathies, and dental aplasia. However, without alkylating chemotherapy as preconditioning, patients usually have graft rejection or limited T cell and no B cell recovery. Thus, addition of normal DCLRE1C cDNA to autologous hematopoietic stem cells is an attractive strategy to treat ART-SCID. We designed a self-inactivating lentivirus vector containing human Artemis cDNA under transcriptional regulation of the human endogenous Artemis promoter (AProArt). Fibroblasts from ART-SCID patients transduced with AProArt lentivirus showed correction of radiosensitivity. Mobilized peripheral blood CD34+ cells from an ART-SCID patient as well as hematopoietic stem cells from Artemis-deficient mice demonstrated restored T and B cell development following AProArt transduction. Murine hematopoietic cells transduced with AProArt exhibited no increase in replating potential in an in vitro immortalization assay, and analysis of AProArt lentivirus insertions showed no predilection for sites that could activate oncogenes. These efficacy and safety findings support institution of a clinical trial of gene addition therapy for ART-SCID.